BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) UK Patent Application (19) GB (11) 2 240 041 (13) A

(43) Date of A publication 24.07.1991

(21) Application No 9028013.2

(22) Date of filing 24.12.1990

(30) Priority data
(31) 8929076 (32) 22.12.1989 (33) GB

(71) Applicant
Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.)

(Incorporated in France)

52/53 rue du Docteur Blanche, 75016 Paris, France

(72) Inventors
Pierre Braquet
Pierre-Etienne Chabrier de Lassauniere
Jean-Michel Guillon
Michel Auguet

(74) Agent and/or Address for Service
Serjeants
25 The Crescent, King Street, Leicester, LE1 6RX, United Kingdom

(51) INT CL[5]
A61K 31/195 31/04

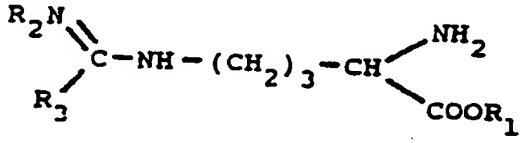
(52) UK CL (Edition K)
A5B BHA B40Y B401 B41Y B411 B412 B413 B44Y B441 B48Y B480 B481 B482 B483 B52Y B523 B55Y B551 B57Y B575 B58Y B586 B66Y B664 B822 B823
U1S S2415

(56) Documents cited
GB 1525765 A GB 1195612 A WO 88/06035 A
Chem. Abs. 114: 35706j
Chem. Abs. 106: 219620t & JP62039524
Chem. Abs. 106: 125905n & JP61275216
Chem. Abs. 98: 221812s & JP57200361
Chem. Abs. 98: 78165s & JP57197211
Chem. Abs. 97: 61070x & JP57081409
Chem. Abs. 78: 75877k & FR2115060

(58) Field of search
Online databases: CHABS, BIOSIS, MEDLINE

(54) Agents for blocking endothelin derived relaxing factor

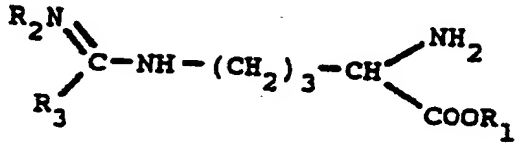
(57) L-aminoacids of the formula



(R_1 = H, CH_3, C_2H_5; R_2 = H, NO_2; R_3 = NH_2, $NHCH_3$, NHC_2H_5, CH_3, C_2H_5) are useful for the treatment of shock states. Particular benefit is obtained by mixing the L-aminoacids with a cyclooxygenase blocker such as indomethacin or aspirin, and such compositions are claimed.

GB 2 240 041 A

In particular, the blocking agents with which th invention is concerned are L-aminoacids of the general formula I



I

wherein R_1 represents a hydrogen atom or a methyl or ethyl group, R_2 represents a hydrogen atom or a nitr group and R_3 represents an amino, methylamino, ethylamino, methyl or ethyl group. These L-aminoacids are known compounds, having been disclosed in EP 230037 and other publications. However, their known use is as cytoprotective agents. We have found that these L-aminoacids are able to restore depressed response to catecholamines and to effectively inhibit vascular hyporeactivity.

Accordingly the invention provides use of an L-aminoacid as above defined for the preparation of a medicament for the treatment by perfusion of shock states.

The preferred L-aminoacids for this use are L-2-amino-5-(1-methylamino-1-imino-methylamino)-pentanoic acid (I : $R_1 = R_2 = H, R_3 = NHCH_3$) which is also known as L-N-monomethyl-arginine and is hereinafter referred to as "L-NMMA";

L-2-amino-5-(1-imino-ethylamino)-pentanoic acid (I : $R_1 = R_2 = H$, $R_3 = CH_3$) which is also known as L-iminoethyl--ornithine and is hereinafter referred to as "L-N10"; and

methyl L-2-amino-5-(1-nitroimino-1-amino-m thylamino)--pentanoate (I : $R_1 = CH_3$, $R_2 = NO_2$, $R_3 = NH_2$) which is also known as L-nitroarginine methyl est r and is hereinafter referred to as "L-NAME".

In some experiments, the endothelium was gently disrupted (-E). Phenylephrine (PE) induced contraction was stable over the time in control rings of animals receiving saline solution (0.9 % NaCl) with (E+) or without (E-) endothelium. The arginine derivative (10, 30 or 100 μM) had no significant effect per se.

Adversely, rings from animals treated with endotoxin showed, despite a similar contractile effect to PE, a loss of tonicity within the time referred as vascular hyporeactivity. This phenomenon was accentuated with intact endothelium (E+). The compounds of the invention (at 10, 30 or 100 μM) were able to reverse the loss of tonicity indicating that these compounds could inhibit the vascular hyporesponsiveness in preparations with or without endothelium.

The effect of the compounds of the invention was specific to the inhibition of EDRF generation whereas L-arginine, the natural precursor of nitric oxide, enhanced the loss of tonicity in endotoxin treated preparation.

In some experiments, the compounds of the invention were introduced in the bath 105 mn after PE when the tissue has completely its tonicity. In these conditions, the compounds of the invention, alone, were able to curatively and totally restore the contraction and therefore contribute extensively to vascular hyporesponsiveness to vasoconstrictor agents in shock. It has been also found that the action of the compounds of the invention might be strongly increased when associated to blockers of cyclooxygenase such as aspirin and indomethacin for instance. This was videnced by the following in vivo experimentation.

TOXICITY

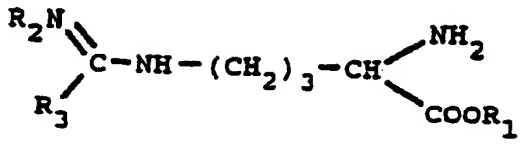
An acute toxicity study of the compounds of this invention has been conducted on rats and mice but no death was noticed at the maximum administrable dosis.

POSOLOGY

For the treatment of shock the usual posology comprises the administration by perfusion of 10 to 500 mg/hour, dissolved or suspended in a serum, of the select d compound of the invention, when used alone. The duration of treatment has to be determined in each case in relationship with a sufficient recovery of the patient. In case of co-administration of one of the compounds according to the invention with a blocker of cycloogenase, the dose for one hour of perfusion contains 10 to 100 mg of the selected compound according to the invention, associated with, 0.1 to 1 mg, if indomethacin is used, or 2 to 200 mg, if aspirin is used, or the corresponding amounts of other blockers of cycloogenase.

CLAIMS

1. Use of an L-aminoacid of the general formula



wherein R_1 represents a hydrogen atom or a methyl or ethyl group, R_2 represents a hydrogen atom or a nitro group and R_3 represents an amino, methylamino, ethylamino, methyl or ethyl group for the preparation of a medicament for the treatment by perfusion of shock states.

2. Use of L-2-amino-5-(1-methylamino)-1-imino-methylamino)--pentanoic acid for the preparation of a medicament for the treatment by perfusion of shock states.

3. Use of L-2-amino-5-(1-imino-ethylamino)-pentanoic acid for the preparation of a medicament for the treatment by perfusion of shock states.

4. Use of methyl L-2-amino-5-(1-nitroimino-1-amino--methylamino)-pentanoate for the preparation of a medicament for the treatment by perfusion of shock states.

5. A pharmaceutical composition comprising an L-aminoacid as defined in claim 1 in admixture with a cyclooxygenase blocker and with a pharmaceutically acceptable diluent or carrier.

6. A pharmaceutical composition comprising L-2-amino-5--(1-methylamino-1-imino-methylamino)-pentanoic acid) in admixture with a cyclooxygenase blocker and with a pharmaceutically acceptable diluent or carri r.